Guidance for Industry

M4: The CTD — General Questions and Answers

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

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ICH

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I. INTRODUCTION

This is one in a series of guidances that provide recommendations for applicants preparing the Common Technical Document for the Registration of Pharmaceuticals for Human Use (CTD) for submission to the U.S. Food and Drug Administration (FDA). This guidance provides answers to questions that have arisen since the finalization of the harmonized CTD guidance documents in November 2000. This guidance addresses general questions about the CTD. Other question and answer (Q & A) guidances are under development to address questions related specifically to quality, safety, and efficacy. The questions and answers provided here reflect the consensus of the ICH parties.

II. BACKGROUND

The guidance for industry issued in November 2000 on preparing the CTD was divided into four separate documents: (1) M4: Organization of the CTD, (2) M4Q: The CTD — Quality, (3) M4E: The CTD — Efficacy, and (4) M4S: The CTD — Safety. Since implementation of these guidances, a number of questions regarding the various CTD documents have been submitted to

[1] This guidance was developed within the M4 CTD Implementation Working Group of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and has been subject to consultation by the regulatory parties, in accordance with the ICH process. This document has been endorsed by the ICH Steering Committee at *Step 4* of the ICH process, September 12, 2002. At *Step 4* of the process, the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan, and the United States.

the various ICH regions. The ICH has developed a process for responding to questions submitted to the ICH Web site.

III. QUESTIONS AND ANSWERS

Q1: Format or Content?

Will a dossier using the CTD format (Modules 2 to 5) be identical for all regions?

A1: Not necessarily. The CTD provides a common format for the submission of information to regulatory authorities in the three ICH regions. However, the CTD does not address the content of submission. There are many regional requirements, as well as applicants' preferences, that could affect the contents of dossiers submitted in each region.

Q2: Expert Reports

Are expert reports still required for submissions under the CTD format?

A2: No. Expert reports are replaced by Module 2. For specific European requirements regarding experts' signatures, please refer to the European Commission Web Site.

Q3: Tables of Contents and Pagination

For a paper CTD submission, the guidance states that for the comprehensive Table of Contents (TOC) in Module 1, no page numbers should be used. Does this apply only to the TOC in Module 1, or for all TOCs in every module? Also, besides the volume numbers and tab identifiers, should the module numbers also be included? For Modules 3, 4, and 5, should the volume number be part of the Table of Contents?

A3: There are no specific guidelines for the page numbers of the TOC. Module numbers, volume numbers, and tab dividers should be part of all TOCs.

Q4: How to Paginate Literature References

When provided, how should literature references be paginated in a paper CTD? Should each reference start with page 1, or should the page number from the source (journal, abstract, etc.) be the only page number included?

A4: Literature references should be paginated according to the page numbering of the source (journal, abstract, etc.).

Q5: Subheading numbering, or numbering within sections

How should subnumbering within a document be organized? Some documents can be up to 50 pages in length with no defined CTD guidance heading and potentially, therefore, no TOC entries or bookmarks (in the electronic version). Some guidance would be welcome to avoid regional interpretations on what is considered acceptable.

A5: Within the document, the applicant can use section numbers at a lower level than those specified in the CTD guidance. However, there should be no other headings appearing in the overall TOC going below the numbering given in the CTD guidance.

For example, for section 3.2.P.3.3, it would be possible to use subsequent numbers (3.2.P.3.3.1, 3.2.P.3.3.2, etc.) to provide further navigation within the document. These should not appear in the overall TOC but can be included as bookmarks within the PDF files.

Q6: Titles of Documents Within Sections (e.g., Reports)

In the header or footer of each document in a dossier, the appropriate TOC title entry should be included. In the case of, for example, a clinical report, the TOC entry is the title of the report and this can be really long. Would the use of the report number (alone) be considered sufficient? In other words, can the layout of the pages throughout the dossier be different: one page layout for reports and another one for Quality sections?

A6: It is recommended that a distinct identifier be put in headers/footers on every page. However, it does not need to be the full title. An abbreviation would suffice.

Q7: Cross-References/Cross-Strings (in Paper Submissions)

It is stated in the CTD that the section should be indicated in cross-strings. What is meant here: The section number, or the section number and section name? (In many cases, the section name is way too long to indicate in a cross-string.)

A7: For the sake of clarity and ease for the reader/reviewer, it is recommended that in paper submissions both the title and the section number be indicated in cross-references (or cross-strings). (However, the cross-reference does not need to indicate the full title; an abbreviation would suffice.)

Q8: General Glossary of Terms

Will there be a general glossary of recommended terminology for use in the CTD?

A8: No glossary of terms is planned at this time.

Q9: Location of the information on Biological Comparability
A combined comparability section might be beneficial to the review process. Is it possible to consider a modification to the CTD to provide for such a section for Biological products?

Currently, comparability data should be included under 2.3.S32/3; preclinically as proposed; and clinically under 2.5.2 and 2.5.6. Each part should summarize briefly the conclusions from the other sections.

- ***In the clinical summary, antigenicity should go under either 2.7.4.3 or 2.7.4.4.***
- ***In the clinical summary, "AEs of special interest" and "Mortality and Hospital Re-admission" should go under 2.7.4.2.1.4 (Other significant AEs).***

A9: No, for the moment the ICH does not foresee a separate CTD section combining all the comparability data.

Q10: Information for Generic Drug Applications

Should the preclinical and clinical summary sections of the CTD be included in applications for generic drug approvals? More specifically, are Modules 4 and 5 of the CTD applicable to abbreviated new drug applications (ANDAs) in the United States and Abridged Marketing Authorization applications in the European Union? Both categories of applications apply to generic drug applications, which ordinarily provide preclinical and clinical data based on available literature.

A10: The CTD provides a format for the submission of information to regulatory authorities. It does not define content. Please refer to region-specific requirements to determine content requirements for the specific submission.